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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/663,497
Filing Date: September 15, 2003
Appellant(s): MCINTIRE ET AL.

Pamela J Sherwood
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 04/13/2009 appealing from the Office action mailed 10/29/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Kroese et al. Genetics in Medicine, 2004, vol. 6, pp. 475-480

Lucentini, The Scientist, 2004, vol. 18, pg. 20

Ionnidis, Plost Med, 2005, vol. 2, no. 8, e124

Hattersley et al. Lancet, 2005, vol. 366, pp. 1315-1323

Hegele, Arth. Thromb. Vasc. Biol, 2002, vol. 22, pp. 1058-1061

GeneCard, HAVCR1, hepatitius A virus cellular receptor, available at www.genecards.org, pp. 1-11

Noguchi et al. Genes and Immunity, 2003, vol. 4, pp. 170-173

Umetsu et al. Ann NY Acad Sci, 2004, vol. 1029, pp. 88-93

Graves et al. J Allerg Clin Immunol, 2005, vol. 118, pp. 650-656

McIntire, Nature, 2003, vol. 425, pp. 576

Sizing et al., J. Immunol, 2007, vol. 178, no. 4, pp. 2249-61

Chae et al., Hum Immunol, 2003, vol. 64, no. 12, pp. 1177-82

Gao, J. Allergy Clin Immunol., 2005, vol. 116, no. 3, p. 650-6

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 – 1st Paragraph – Scope of Enablement

Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for determining a Caucasian or Asian's predisposition to atopy protection by detecting the presence of homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protect against atopy, does not reasonably provide enablement for a method for screening for a human individual's predisposition to any atopy by analyzing for the presence of any TIM-1 polymorphism. This rejection was previously presented in section 8 of the previous office action mailed 03/05/2008 and is reiterated below.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the screening for a human individual's predisposition to atopy by analyzing the presence of at least one TIM-1 polymorphism wherein the presence of the polymorphism is indicative of an individual's predisposition to develop an atopy. The claims are further drawn to a method of contacting a biological sample with a probe that specifically binds to the nucleic acid sequence of MTTTVP or a polymorphism in exon 3 of TIM-1 gene and further comprising the step of analyzing an individual for the presence of hepatitis A virus seropositivity.

The rejected claims encompass analysis of a human. The rejected claims encompass any type of atopy and detection of any polymorphism in TIM-1.

The nature of the claims requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop atopy.

Guidance in the Specification and Working Examples

The specification asserts that polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus(HAV) are shown to be associated with protection from the development of immunological disorders, such as atopy. The specification asserts that a common polymorphism of TIM-1 in major human population has an insertion at position 157, 157insMTTTVP and HAV seropositivity protects against atopy but only in individuals with 157 insMTTTVP allele. The specification asserts that in some aspects the atopic disease is allergic rhinitis, atopic dermatitis, or asthma (see page 2, paragraph 6).

The specification asserts that polymorphisms in the coding region of human TIM1 include an insertion, 157insMTTTVP (allele 1), a deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D (see paragraph 37, page 8-9) and assert that most of these variations are located within exon 3. The specification asserts that Tim gene sequence is other than human Tim-1, allele 1. The specification asserts that in combination with HAV seropositivity, allele 1 is protective for atopy and the presence is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis and determination of the presence of the allele may be determined by various methods known in the art (see page 10, paragraph 42). Although determination of allele is routine in the art, predictably correlating an allele to atopy in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with atopy in any human individual.

The specification teaches there are a number of methods that are available for analyzing nucleic acid for the presence of a specific sequence. The specification teaches that amplification with detectable labels, oligonucleotide ligation, hybridization to any array are available (see paragraph 53-54, 56, pages 13-14). However, the specification does not predictably correlate a method for screening for predisposition to atopy in any human by detecting "any" polymorphism within the TIM-1.

The specification demonstrates a working example of association between atopy and 157insMTTTVP in a cross-sectional study of 375 individuals who were tested for serologic evidence of atopy and prior HAV infection. The specification demonstrates that HAV infection protects against atopy but only in individuals with the 157insMTTTVP Tim-1 allele (see paragraph 194, pages 54-55). Although, table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTTVP Tim-1 allele are associated with protection against atopy, table S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and that are homozygous for the 157insMTTTVP allele. Table S4 demonstrates that neither the HAV negative or HAV positive population of Asians subjects is statistically relevant to diagnosis a predisposition to any immunological disorder or atopy and Table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasians subjects with HAV that are homozygous for 157insMTTTVP allele. The specification asserts that the African American sample size was too small to present separately (see paragraph 199, page 56).

The specification does not teach the association of any polymorphism, other than the 157insMTTTVP allele, in TIM-1 gene with the risk of developing atopy. The specification does not teach an association of any polymorphism with an increased likihood of developing atopy.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphisms other than 157insMTTVIP allele of the TIM-1 gene is predictably correlative to diagnosing a predisposition to atopy in all ethnicities. The specification teaches only a statistically relevant association of 157insMTTTVP in Caucasian subjects that are homozygous for the allele that are HAV positive and have protection against atopy. The specification does not teach an association with any other polymorphism with TIM-1 and any atopy or association with presence or absence of HAV. It is unclear which polymorphism would be predictive of screening for predisposition to atopy in "any" individual.

The specification envisions hypothetical situations where any polymorphism within the TIM-1 gene could determine the presence of atopy. The specification appears to be conceiving of possible scenarios where the presence of any polymorphism in TIM-1 would indicate the presence – or absence – of atopy, however, it is unclear how one of skill in the art would determine which polymorphism of TIM-1 gene would screen for predisposition to atopy.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in TIM-1 gene and predisposition in any individual for atopy.

While the claims of the instant application are broad and encompass analysis of any human, the instant specification provides evidence only of a statistically significant association between the 157ins MTTTVP allele of TIM-1 of SEQ ID No. 22, and protection against atopy in Caucasians that are positive for HAV.

Because the claims are drawn to methods that encompass the analysis of any polymorphism of TIM-1 gene, it is relevant to note that there are multiple polymorphic positions identified in TIM-1. A Gene Card search of TIM-1 gene indicates that there are 135 SNPs of TIM-1 gene (see page 7 of Gene Card). The instant specification does not teach any association of these 135 polymorphisms with atopy.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the

evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph).

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005,

vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate. It is further relevant to point out that Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with atopy, as the specification does not teach a large sample size or confidence levels greater than 95% for every

polymorphism of the TIM-1 gene or the association of TIM-1 with atopy. The specification only teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in a Caucasian population.

Furthermore, the post filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy. Noguchi et al. (Genes and Immunity (2003) 4:170-173) teach that the seven different polymorphism within the TIM-1 gene, including two insertions and deletions were found not associated with the development of asthma in Japanese asthmatic families that showed strong evidence for linkage of atopic asthma (see page 172, right column, last paragraph). Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph).

Applicant's own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), teach that in the total population there was no association of the TIM-1 insertion (157insMTTTVP) with atopy. Umetsu et al. teach that if an individual had one or two copies of the insertion polymorphism in TIM-1, he or she was as likely to be atopic as those who had no copies of the insertion polymorphism, however when assayed for HAV seropositive and seronegative, it was found that a significant inverse association of the insertion and atopy. Umetsu et al. teach that the HAV seropositive subjects who had one or two copies of the insertion were much less likely to be atopic that those who had no copies and the HAV negative

population was no associated with any protection against atopy. (see page 92, 1st full paragraph). Thus, Umetsu et al. teach that the only individuals that are HAV positive are predictably correlative to protection against atopy in individuals that have the polymorphic insertion in TIM-1 gene.

Graves et al. (J Allerg Clin Immunol 2005, vol 118, pages 650-656) teach a study to evaluate multiple polymorphism in TIM1 gene and the association with atopy. Graves et al. teach association with atopy and one polymorphism, 15bp insertion/deletion of TIM-1 (see page 655, 1st column, 1st full paragraph). Graves et al. teach that in a Korean case control study increased risk for atopic dermatitis was found but not for asthma with the 15bp deletion of the TIM-1 gene (see page 655, 1st column, 1st full paragraph). Graves et al. teach analysis of seven different polymorphisms of TIM-1 gene and demonstrate that several polymorphisms are not statistically relevant, for example TIM1_1, 2, 5, and 7 (see table E2). Graves et al. teach that their findings need to replicated in other studies and the major limitation of the analysis is related to ethnic heterogeneity reflected in the Tucson population. Therefore, Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed.

The claims are broadly drawn to screening for predisposition to any individual of atopy. The example presented in the specification provides an analysis of the 157insMTTTVP allele of TIM-1 gene with regard to HAV positive Caucasians subjects and atopy. The prior art teaches that confidence levels greater than 95% are necessary for predictably associating genetic tests with diseases. The instant specification shows the unpredictability in associating any

polymorphism, including 157insMTTTVP allele of TIM-1 gene with any individual for any type of atopic immunological disorder. For example, table S3 demonstrates that 157insMTTTVP is not associated with atopy protection any individual that is not HAV positive and demonstrates that the 157insMTTTVP is not associated with atopy protection in every ethnic group (see table S4 and lack of African American analysis). Thus, based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with any type of immunological disorder, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with any type of immunological disorder. The specification teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in the TIM-1 in a Caucasian population for protection against atopy.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the TIM-1 gene with any atopic immunological disorder in any individual along with the evidence in the art that demonstrates that not every polymorphism of TIM-1 gene is associated with an immunological disorder, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms of the TIM-1 gene (135 polymorphisms known) to determine if in fact there was either an association between the polymorphism in individuals and atopy. The results of such a study are clearly unpredictable as evidence by the applicant's own post filing art (which reflects the current state of the art) and the

teachings in the specification with regard to correlating the 157insMTTTVP allele of TIM-1 with different ethnic groups and HAV negative individuals to atopy much less any immunological disorder. Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Furthermore, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph). In the instant case, it would be unpredictable as to whether or not 157insMTTTVP would be responsible for determining the predisposition to atopy in any individual without also determining if the individual was HAV positive or negative.

In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine the sequence of the human TIM-1 in each individual and then determine which polymorphism would detect any type of immunological disorder. The skilled artisan would then have to screen variants to determine those that are associated with a susceptibility to any atopic immunological disorder in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any atopy. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Claim Rejections - 35 USC § 112 – 1st Paragraph – Written Description

Claims 1, 4, 7 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in section 8 of the office action mailed 10/04/2007 and is reiterated below.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any individual (claim 1). The claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The claims are limited to probes that specifically bind to exon 3 of TIM-1 gene (claim 23) or probes that bind to MTTTVP sequence (claim 4), however the limitation of probes that specifically bind to a nucleic acid sequence or exon 3 does not limit the claims to detection of a specific polymorphism of TIM-1 gene as the claims merely require analyzing a biological sample with a probe that specifically binds to a nucleic acid sequence and this does not limit the polymorphism that is indicative of atopic immunological disorder. The claims merely require analyzing a probe that binds to a nucleic acid but the claims do not require the presence of the specific probe binding to the nucleic acid is indicative of predisposition to develop an atopic immunological disorder.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1 gene. Thus the claims encompass the detection of any of different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 18, 20, 22, 24, 26, and 28. The specification also provides the amino acid sequence of TIM-1 as SEQ ID No. 19, 21, 23, 25, 27, and 29. The specification provides analysis of the insertion of the following amino acid sequence of MTTTVP at position 157 and indicating that this insertion is indicative of association of disease. The specification does not teach any association with any other polymorphic variation disclosed in the specification, for example deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D that are indicative of association of atopic immunological disorders.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification

provides only the polymorphic sequences of the human TIM1 gene (SEQ ID NO: 18, 20, 22, 24, and 26) and the encoded amino acid sequence (SEQ ID NO: 19, 21, 23, 25, 27). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of atopic immunological disorder based on detection of the non-disclosed gene. Furthermore, the art discloses that there are 135 SNPs known for the TIM-1 gene (see GeneCard, page 7). Neither the specification nor the prior art teach an association with any of these SNPs with any type of immunological disorder or atopy.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of the TIM-1 gene other than the insertion of the amino acid sequence of MTTTVP at position 157 of the amino acid sequence, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of diagnosis for the predisposition of immunological disorder in an individual by determining the presence of a polymorphism in TIM-1 other than methods using detection of the insertion of the amino acid sequence MTTTVP at position 157 of TIM-1.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

(10) Response to Argument

A-Claim Rejections – 35 USC 112, 1st Paragraph – Enablement

The appeal brief filed on 04/13/2009 traverses the rejection. Appellant's arguments have been fully considered but are not persuasive for the reasons which follow.

The appellants assert on page 7, 3rd paragraph that the claims do not encompass correlating the presence of a polymorphism to the development of atopy but rather the claims encompass presence of a polymorphism being indicative of the individual's predisposition to develop atopy. Appellants point to a common TIM-1 polymorphism, 157insMTTTVP and associating its presence to individuals predisposition to develop atopic disorder. Appellants state that they are not claiming every polymorphism in the TIM-1 is related atopy and are limiting the claims to methods of detecting polymorphisms in TIM-1 which information is useful to individuals wishing to evaluate their predisposition to atopy and further evaluate in the context of HAV-1 seropositivity. However, the claims are not drawn merely to detecting polymorphisms in TIM-1 gene or screening for polymorphisms associated with atopy, the claims are drawn to analyzing for the presence of at least one TIM-1 polymorphisms wherein the presence of the

polymorphism is indicative of an individual's predisposition to develop atopy. Therefore, the claims require the correlation that the presence of polymorphisms in the TIM-1 gene is associated with predisposition to develop atopy. The specification does not provide any guidance on which polymorphisms in the large genus of TIM-1 polymorphisms are associated with the large genus of the medical condition, atopy. The specification discloses 7 polymorphisms within TIM-1, however the specification does not provide any guidance that any of these polymorphism other than 157insMTTTVP is associated with developing the large genus of atopy disorder, which encompasses disorders such as asthma, allergic rhinitis, eczema. Additionally, the specification demonstrates that 157insMTTTVP is not associated with developing of atopy but rather demonstrates that in a small subpopulation of Caucasian humans who are HAV+ that the polymorphism is associated with protection against atopy and not predisposition to develop atopy. It is noted that the examiner is not requiring that every polymorphism within the TIM-1 gene is associated with developing atopy but rather that the specification provide guidance so that the skilled artisan would be able to predictably determine which polymorphisms within the large genus of TIM-1 polymorphisms will be predictably associated with developing any type of atopy. For example, the specification does not provide any guidance on a representative number of polymorphisms within TIM-1 gene and their association with development of atopy that would allow the skilled artisan to perform the claimed method which requires detecting polymorphisms in the TIM-1 gene and determining the presence of the polymorphism would be indicative of an individual's development of the large genus of atopy. The specification merely provides sequences of seven polymorphism within the TIM-1 gene however as stated earlier the specification only provides an association study with

157insMTTTVP polymorphism of TIM-1 and demonstrates it is not associated with development of atopy.

The appellants assert on page 7 continued to page 8 that atopy is a distinct medical condition and the art recognizes atopic immunological disorder or atopy as allergic hypersensitivity affecting parts of the body not in contact with the allergen which includes eczema, asthma, allergic rhinitis, and allergic conjunctivitis. The examiner agrees with appellant's explanation of atopy and acknowledges that predisposition to develop atopy or decreased risk of developing atopy includes a large genus of phenotypes, such as eczema, asthma, allergic rhinitis, and allergic conjunctivitis.

The appellants asserts on page 8, 1st two paragraphs, that both the specification and art teach a correlation between TIM-1 polymorphisms and atopy. The appellant's state that the specification describes a common polymorphism, linkage of TIM-1 locus to development of atopy, and analysis of polymorphisms in TIM-1 with atopy. Appellants state that Sizing et al. and Graves et al. corroborate the correlation between detection of the presence of TIM-1 polymorphism and predisposition to atopy. The specification describes seven polymorphisms however the specification provides guidance and analysis of one polymorphism, 157insMTTTVP polymorphism. The working example in the specification provides additional evidence that the presence of a polymorphism within the TIM-1 is not predictably associated with development of atopy as example 6 of the specification demonstrates that 157insMTTTVP is not associated with development of atopy but that the presence of seropositivity of HAV in a Caucasian human is predictably associated with protection against atopy thus demonstrating that the presence of a polymorphism is not associated with development of atopy but rather

protection against development of atopy. Additionally neither Graves nor Sizing provides corroboration of the breadth of the claimed invention. Graves teaches that their findings need to be replicated in other studies and analyze only one polymorphism, 15 bp insertion, which was not disclosed in the instant specification. Sizing teaches that in 2007 the TIM-1 locus was linked to atopic diseases however Sizing demonstrates analysis of TIM-1 gene in mice not humans and the claims are drawn to screening a human's individual predisposition to atopy and therefore Sizing can not be relied upon to corroborate the presence of TIM-1 polymorphisms and predisposition to development of atopy in humans.

Appellants assert that the nature of invention is not complex and the claims are not unduly broad. It is noted that the examiner is not asserting in the rejection that the claims are unduly broad but merely demonstrating the breadth of the claims. It is the position of the examiner that the specification is not enabled for the breadth of the claim.

Appellants state on page 9, last paragraph, the claims do not recite that every polymorphism in TIM-1 is related to an atopic disorder and maintain that the claims are drawn to detecting polymorphisms in the TIM-1 gene which information is useful to an individual wishing to evaluate their predisposition to atopy and which information may be further evaluated in the context of HAV-1 seropositivity. It is noted that the claims are not drawn to methods of detecting polymorphisms in the TIM-1 nor are the claims drawn to methods of determining which polymorphisms in the TIM-1 are indicative of atopy, the claims are drawn to screening a human's predisposition to atopy by the presence of a polymorphism in the TIM-1 gene, thus the claims require the knowledge that the polymorphism is associated with development of atopy. The examiner is not asserting that every polymorphism in TIM-1 is related to atopic disorder,

however the examiner does maintain that the specification does not provide adequate guidance to allow the skilled artisan to make and use the invention as the specification does not provide guidance on which polymorphisms within the large genus of TIM-1 polymorphisms would be predictably associated with developing atopy.

The appellants assert on page 10, 1st paragraph that reduction of practice may be actual reduction or constructive reduction to practice and state that the instant specification shows unambiguous evidence that TIM-1 gene is associated with atopy. The appellants state that the constructive reduction to practice constitute by the present application thus provides both a rationale for selection of TIM-1 gene as a screening tool and a means to effect such screening using Tim-1 alleles in individuals. The specification does not provide unambiguous evidence that polymorphisms in the TIM-1 gene are associated with development of atopy. The specification, in fact, contradicts that the presence of polymorphisms are associated with development of atopy as the presence of 157insMTTTVP in a subpopulation is associated with protection against atopy not development of atopy, thus the specification provides direct evidence that polymorphisms within the TIM-1 gene are not associated with development of atopy. The specification specifically states "as an independent variable 157insMTTTVP is not associated with atopy" see pg. 54, last sent cont'd to pg. 55, first sent.

Although the specification does teach working examples of identification of TIM genes in a mouse model for asthma susceptibility genes (example 1), human TIM sequence (example 2), expression of TIM sequences in human tissue (example 3), generation of antibodies against mouse TIM-1 (example 4), development of a TIM1 knockout mouse (example 5), analysis of 157insMTTTVP polymorphism in atopy in a population that is HAV (-) and HAV (+) (example

6), none of the working examples describe the association of a representative number of polymorphisms within the TIM-1 gene or even the 6 disclosed polymorphisms other than 157insMTTTVP polymorphism that are associated with developing atopy. Furthermore, the specification does not describe any type of functional assay or describe the functionally relevant portions of the TIM-1 gene that would allow the skilled artisan to determine which regions of the gene are important and involved in development of atopy to then determine which polymorphisms to screen. Therefore, the specification does not provide unambiguous evidence that polymorphisms in the TIM-1 gene are associated with development of atopy.

Appellants state on page 10, 2nd paragraph that the instant specification provides detailed description of the location of the TIM gene family, methods to detect polymorphisms in TIM gene, reference publication linking TIM-1 gene to immunological responses and thus provides suitable guidance such that the ordinary artisan can identify polymorphism allelic variants of TIM-1 associated with atopic conditions. Appellants maintain on page 11, last para that the specification provides multiple experimental examples of an association of TIM-1 gene polymorphism with atopy and the art provides multiple working examples of how TIM polymorphisms are associated with atopy. It is noted that the specification does not disclose multiple publications linking TIM-1 gene to immunological responses nor does Appellant provide the references that provide multiple working examples of how TIM polymorphisms are associated with atopy. Additionally, post filing art teaches that even if a gene is associated with involvement of a disorder this does not reason that a polymorphism within the gene will be associated with the disorder (see Hattersly and Hegele).

Appellants maintain that they have provided statistically relevant evidence supporting a predictable correlation between the TIM-1 polymorphism in multiple populations, the validity of which was confirmed by peer review and subsequent publication in a leading journal in the art, McIntire et al. and the specification supports the pending claim element of method of screening for human individual's predisposition to atopy. Appellants state on page 12, 2nd paragraph that the subgroup for Caucasian and Asian population for the 157insMTTTVP reports significant P values for HAV + individuals as such the 157insMTTTVP allele is predictably correlative for the group including seropositive homozygous and heterozygous individuals in both Caucasian and Asian population and assert it is unclear why the office action states the data is not statistically relevant. The data presented in table S3 and S4 in the specification demonstrates that in a small population the presence of 157insMTTTVP is not associated with protection against atopy. For example, in the large population the presence of 157insMTTTVP in a HAV + population is associated with protection against atopy (see S2) however analysis of smaller populations, Caucasian and Asian population demonstrate that the polymorphism is not associated in all populations. The analysis of the polymorphism associated with atopy is only powered when the alleles of the 157insMTTTVP polymorphism are grouped together and the data demonstrates that in a smaller population there is no association (see table S4), therefore how could one determine if one individual is associated with predisposition to atopy with the presence of a polymorphism? Take for example table S4, there are 51 individuals that are Asian and HAV +, however only 1 is homozygous, 11 are heterozygous, and 24 have neither allele for nonatopic individuals. The statistical analysis of the one individual that is homozygous has a p value of .113 and an odds ratio of .104, therefore this exemplifies the unpredictability of determining one individual's

predisposition to developing atopy and demonstrates that the data is not statistically relevant. The claims are not limited to analysis of a large population of individuals to determine the association of the polymorphism with atopy but rather encompass analysis of one individual and determining their predisposition to develop atopy. As demonstrated by the working example, the ability to determine one individual's risk of developing atopy or protecting against atopy is not statistically relevant as the p value is greater than .05 and the odds ratio is .104. Additionally, the data demonstrates that the smaller the population the less likely the association of the polymorphisms with protection against the disorder (see population size of data analysis of S2, S3, and S4). Although the specification asserts that there is no significant difference between either the Caucasian or Asian population, this analysis is based on the presence of combined data for both heterozygous and homozygous and the appropriate comparison would be the analysis of the individual genotypes (comparison of homozygous (2 vs. 0 allele column) and heterozygous (1 vs. 0 allele column) for both populations). Comparison of homozygous and heterozygous genotype analysis in each population demonstrates that only the homozygous allele in a Caucasian population that is HAV + is statistically associated. All other populations have p values greater than .05. Furthermore, the claims are not drawn to method of screening an individuals decreased risk of atopy but rather method of screening individuals risk of developing atopy and thus the example demonstrates that the presence of the polymorphism, 157insMTTTVP is not associated with determining risk of developing atopy but rather demonstrates that in a Caucasian HAV+ population the polymorphism it is associated with protection against atopy. It is noted that appellants did not address the discrepancy of the p values among the homozygous and heterozygous genotypes in the Asian and Caucasian

population when raised in the office action mailed 3/5/08 and summarized by appellants on page 13 of the brief.

With regard to appellants assertions that they have proven the validity of their statistical analysis by publishing in the esteemed journal the same data being challenged by the office (see McIntire et al. (2003)), it is noted that the publication did not drawn the conclusion that polymorphisms within the TIM-1 gene are associated with development of atopy. The journal article concluded that HAV seropositivity protects against atopy but only in individuals with the insertion of 157insMTTTVP variant in TIM-1. Thus, McIntire provides direct evidence which contradicts instant claim 1 and claim 20 which requires the presence of a polymorphism is indicative of development of atopy. Additionally, the journal article does not present the same data presented in the specification. For example, the data presented in table S3 and S4 of the specification was not submitted to the journal article. Therefore, the validity of the statistical analysis of the data presented in the specification was not peer viewed. Furthermore, claim 1 and 20 are drawn to predisposition to developing atopy by detection of polymorphism in TIM-1 gene and specific polymorphism in TIM-1 gene, 157insMTTTVP however McIntire as well as the specification exemplify that this polymorphism has a protective effect and is not associated with development of atopy.

The appellant's state on page 16 cont'd to page 17 that the level of predictability with regard to the association of TIM-1 polymorphism with atopy phenotype in an individual is in fact reasonably high as evidence by the relevant pre and post filing art (Chae, Graves and Gao et al). However Chae, Graves, and Gao provide specific evidence that polymorphisms in the TIM-1 are not associated with predisposition to develop the large genus of atopy phenotypes and

demonstrate the unpredictability of determining which polymorphisms within TIM-1 will be predictably associated with atopy. For example, Chae demonstrates that one polymorphism is associated with asthma within TIM-1 however another variant 5385_5397 del is not associated. Graves demonstrates that multiple polymorphisms are not associated with atopy and teach further studies need to be completed. Nogushi teach no observation between TIM-1 polymorphisms and atopic asthma in a Japanese asthmatic families and teach further studies in different populations are needed. Gao demonstrate that African Americans that do not have the MTTTVP insertion are predictably associated with asthma (i.e. the *absence* of the polymorphism is associated with asthma, type of atopy) which is the opposite of the claimed method as the claims are drawn to the presence of a polymorphism is indicative of developing atopy (claim 1) and additional claims specifically require detection of 157insMTTTVP (claim 20).

Appellants maintain that techniques for generating probes with specificity for any of the TIM-1 SNPs is routine in the art and thus the method is highly predictable. The examiner agrees that generating probes with specificity for any TIM-1 SNP is routine in the art, however associating polymorphisms in the TIM-1 gene with atopy is unpredictable. The examiner demonstrated the number of known SNPs for TIM-1 gene to provide evidence of the large genus of "at least one polymorphism in TIM-1 gene" (see GeneCard) and demonstrate that the specification does not provide a representative number of the large genus of TIM-1 polymorphisms and their predictable association with the large genus of atopy phenotypes.

Appellants state on page 19 that the major finding of the exemplified reduction to practice, the association of protection against atopy with 157insMTTTVP allele in the presence of HAV seropositivity is presented with p values >95% confidence and points to table 1.

Appellants assert that the critical findings presented in table S2 through S4 likewise meet this standard as such the recommendation by Kroese and prior probability of Lucenti is met. The recommendations with regard to SNP association studies of Kroese, Hegele, Ionnidis, and Hattersley have not been met. For example, the data in tables S3 and S4 demonstrate p values above .05 and odds ratio well below 2 (for example .103, table S4) for protection against atopy in the presence of HAV (+) in Asian population and in Caucasian that carry the heterozygous allele. Ionnidis demonstrates that the totality of the evidence is what matters and statistical significance of a single study only gives a partial picture (see pg. 701, 1st column). Hattersly teach that odds ratio of 1.1 to 2.0 require the number of controls to be in the thousands. In the instant application, the number of controls is from 50-150 and the odds ratio is well below 2.0 for analysis. Additionally, Hegele demonstrate that it unpredictably to associate a genotype with a phenotype and teaches the desire to have a known or putative functional domain for functional consequence and the specification does not disclose a functional domain of TIM-1. Additionally, recommendation by Kroese nor Lucentini are not met for the subpopulations (see table S3 and S4). The claims broadly encompass analysis of the presence of a polymorphism (or specific polymorphism 157insMTTTVP claim 20) and the presence of a polymorphism in TIM-1 being indicative of developing atopy and the specification demonstrates that 157insMTTTVP is not associated with developing atopy and only provides an indication of protection or decreased risk with seropositivity of HAV. Additionally the specification states that "157insMTTTVP is not associated with atopy" with a p value is .142 (see pg. 54-55, last sent), therefore the presence of a homozygous 157insMTTTVP in seropositivity Asian population is not associated as the p value is .113 (see table S4).

The appellants state that the instant example 6 demonstrates a correlation between TIM-1 gene polymorphism and allergic rhinitis, atopic dermatitis, and food allergy and positive for specific IgE against local allergens, not for familial asthma. Appellant conclude based on this assertion that there is no apparent contradiction between Nogushi and the present example as Nogushi analysis is toward familial asthma. Appellant restate that the instant application is not claiming that every polymorphism must carry predictive association with atopic disease. However, the specification does not define atopy and the claims are not limited to allergic rhinitis, atopic dermatitis, food allergies or local allergens and thus familial asthma falls within the large genus of atopy. Therefore, Nogushi is relevant to cite to demonstrate specific evidence that it is unpredictable to associate the presence of a polymorphism in the TIM-1 gene wherein the presence is indicative of developing atopy, as Nogushi teaches no association with TIM-1 polymorphisms and asthma. As stated previously, the examiner is not requiring that the specification provide guidance that every polymorphism in the TIM-1 gene is associated with atopic disease, however the specification must enable the claimed invention. In the instant case, the specification does not providence a representative number of polymorphisms associated with atopic disease that would provide guidance to the skilled artisan to predictably determine which polymorphisms are associated with atopic disease to determine an individuals predisposition to atopy.

Appellants state on page 23 that Umetsu is in fact confirming the instant application that HAV+ insertion allele carriers are protected against atopy while HAV- carriers are not. However, Umetsu demonstrates in the total population there was no association of the TIM-1 association, 157insMTTTVP with atopy and teaches that individual with one or two copies of the

insertion are just as likely to be atopic as those who had no copies, which provides specific evidence that the presence of polymorphisms in the TIM-1 gene are not indicative of developing atopy (instant claim 1 and claim 20).

Appellants assert that the state of the art is sufficiently well developed, the level of predictability is sufficiently high, and the level of skill in the art is high that one of skill in the art would be able to practice the claimed invention. Appellants state that there is ample guidance and working examples to make and use the claimed invention. However, Umetsu, Gao, Graves, and Nogushi provide specific evidence that at the time the invention was filed it would have been difficult to predict which, if any, polymorphism in the TIM-1 gene are associated with developing atopy. Without disclosure of specific structures and functional assays to determine which polymorphisms are associated with atopic disorders, the skilled artisan would have to perform an extremely large study and include different populations to determine if in fact there was either an association between each polymorphism with any type of atopy as well as determine the association between the presence of HAV and each polymorphism. The unpredictability of the field of detecting risk of disease from genetic polymorphisms, the amount of work needed to determine associations between polymorphisms and risk of disease, the breadth of the Appellant's claims and the lack of disclosure of specific polymorphisms associated with developing atopy, indicate that carrying out the claimed method would require undue experimentation. Appellant's specification does not disclose a single polymorphism that would lead to developing atopy. While the specification demonstrates a relationship with the presence of homozygous 157insMTTTVP in a Caucasian population that are seropositive for HAV are protected against atopy there is no additional direction as to how one skilled in the art would

have determine polymorphisms that would lead to developing atopy. "It is not enough that a person skilled in the art, by carrying on investigations along the line indicated in the instant application, and by a great amount of work eventually might find out how to make and use the instant invention. The statute [35 USC 112, 1st para] requires that the application itself to inform, not direct others to find out for themselves," *Application of Scarbrough*, 200, F.2d 560, 565 (CCPA 1974).

B-Claim Rejections – 35 USC 112, 1st Paragraph – Written Description

The appeal brief filed on 04/13/2009 traverses the rejection. Appellant's arguments have been fully considered but are not persuasive for the reasons which follow.

The appellants assert that the claims are drawn to methods of screening individual's for disposition to atopy and atopy is well characterized with underlying immune dysfunction which manifests in specific clinical phenomenon. The appellants assert that they have unambiguously proven the link between TIM-1 and atopy and point to the working examples in the specification, have describe TIM-1 and related genes, provided common polymorphisms in TIM-1 and linkage of TIM-1 locus to development of atopy. This is not found persuasive as the working examples in the specification demonstrate that only one polymorphism, 157insMTTTVP in a Caucasian population that is HAV (+) is associated with protection against to atopy. Although the claim is drawn to methods of screening individuals for disposition to atopy the claim requires detecting a polymorphism in the TIM-1 gene and the presence of the polymorphism is indicative of predisposition to develop atopy, therefore the claims require the knowledge of a correlation between the polymorphism in the TIM-1 gene and predisposition to atopy. The specification

does not describe a representative number of polymorphisms in the TIM-1 gene that are associated with atopy disposition. The specification discloses 7 polymorphisms in TIM-1 gene (see para 172) however the specification does not describe the functional importance with regard to TIM-1 and atopy activity of these polymorphisms nor the association of the polymorphism with atopy. The working examples in the specification describe identification of TIM genes in a mouse model for asthma susceptibility genes (example 1), human TIM sequence (example 2), expression of TIM sequences in human tissue (example 3), generation of antibodies against mouse TIM-1 (example 4), development of a TIM1 knockout mouse (example 5), analysis of 157insMTTTVP polymorphism in atopy in a population that is HAV (-) and HAV (+) (example 6). However none of the working examples describe association of a representative number of polymorphisms within the TIM-1 gene or even the 6 disclosed polymorphisms other than 157insMTTTVP polymorphism that are associated with atopy. Furthermore, the specification does not describe any type of functional assay or describe the functionally relevant portions of the TIM-1 gene that would allow the skilled artisan to determine which regions of the gene are important and involved in development of atopy to then determine which polymorphisms to screen.

Appellants assert while there may be sequence within the genus defined by TIM-1 polymorphism which will not significantly associate with atopy the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work. The appellants assert that one of skill in the art would recognize that a reasonable correlation between atopy and members of this genus is readily established by the disclosure of the instant application and since every species

does not have to be tested for the genus to be enabled, extensive per sequence disclosure or guidance regarding the active species in the genus does not have to be provided in order for a genus of this scope to be enabled. The examiner is not suggesting or requiring applicant to provide every species of the large genus of TIM-1 polymorphisms encompassed by the claims, however a representative number of the claimed genus must be described. In the instant case, the claims require polymorphism within or specific to TIM-1 gene that are associated with atopy however a representative number of nucleic acids of this large genus of polymorphisms in the TIM-1 gene that are associated with atopy is not described in the specification. The specification merely discloses 7 polymorphisms, however the specification only describes one polymorphism in a very specific subpopulation that is associated with protection against atopy not predisposition to develop atopy, the specification provides no guidance on how the skilled artisan would be able to predictably correlate which polymorphisms within the TIM-1 gene would be associated with atopy in a given population. For example, the one polymorphism that is described, 157ins MTTTVP, is demonstrated to only be associated with protection against atopy in a Caucasian population that is HAV(+). Therefore, even the one polymorphism described in the specification is not associated with atopy in all populations, which demonstrates the unpredictability of the structure function correlation of the genus of the claimed invention and the specification has not described a representative number of polymorphic species of TIM-1 that are associated with atopy.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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